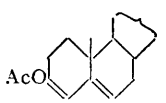
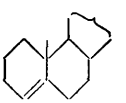
520. *New Cholestene Diols. The Simultaneous Action of Aluminium Hydride and Aluminium Chloride on the Enol Acetate of Cholest-4-en-3-one.*

By B. R. Brown.

The simultaneous action of aluminium hydride and aluminium chloride on the enol acetate (I) of cholest-4-en-3-one in ether yields cholest-4-ene (II), cholest-4-en-3-one, and a molecular compound of two cholestene diols. The evidence available only permits tentative formulation of these diols. This is the first recorded use of the mixture aluminium hydride–aluminium chloride as a reagent.

Dauben and Eastham (*J. Amer. Chem. Soc.*, 1951, **73**, 3260) have reported that the reduction of the enol acetate (I) of cholest-4-en-3-one with lithium aluminium hydride yields cholesterol, *epi*cholesterol, cholest-4-en-3α-ol, cholest-4-en-3β-ol, and cholest-4-en-3-one. This observation has been confirmed, and it is found that aluminium hydride brings about

(I)   (II)

reduction in the same way. However, the action of aluminium hydride in the presence of excess of aluminium chloride causes the reaction to follow a different course, the products being cholest-4-ene (II) (16%), cholest-4-en-3-one (20%), and a molecular compound, $C_{27}H_{46}O_2$, m. p. 196—197° (49%). The action of aluminium chloride alone on the enol

acetate in ether produces an almost quantitative yield of cholest-4-en-3-one. There appears to be no previous record of the use of the mixture aluminium hydride–aluminium chloride as a reagent. However, from their lithium aluminium hydride reduction Dauben and Eastham (*loc. cit.*) isolated up to 2% of a diol, $C_{27}H_{46}O_2$, m. p. 168—169°. This may be an impure specimen of the molecular compound or, more likely, of one of its component diols.

Acetylation of the molecular compound followed by fractional crystallisation of the product yields two acetates. These on hydrolysis give two diols of formula $C_{27}H_{46}O_2$ (A) m. p. 177—178° from the acetate of m. p. 157—158°, and (B), m. p. 179—180° from the acetate of m. p. 112—113°. Recombination of these diols in equimolecular amounts yields the original molecular compound, as does hydrolysis of an equimolecular mixture of the two acetates. Moreover, the specific rotation of the molecular compound ($[\alpha]_D$ −47°) is very nearly half the sum of the rotations of the diols (A) ($[\alpha]_D$ −64°) and (B) ($[\alpha]_D$ −34°).

The diols (A) and (B) yield diacetates and dibenzoates, and active hydrogen values give further evidence of two hydroxyl groups.

The negative values of molecular rotation indicate the presence of a double bond in each of the diols (A) ($[M]_D$ −257°) and (B) ($[M]_D$ −137°). This is confirmed by reaction with bromine, and by titration with perbenzoic acid corresponding to one double bond in each diol. From the latter reaction an epoxide of the molecular compound has been isolated. The large negative values of molecular rotation indicate that each diol contains a double bond in the 5 : 6- or 6 : 7-position (see Barton and Klyne, *Chem. and Ind.*, 1948, 755, Barton and Rosenfelder, *J.*, 1949, 2459, and Wintersteiner and Morse, *J. Amer. Chem. Soc.*, 1950, **72**, 1923, for the contribution of double bonds to molecular rotation). Since the double bond is in the 5 : 6-position in the original enol acetate (I), it probably occupies this position also in the product. However, this double bond must be hindered in some way, since its complete saturation with bromine is slow (5—10 minutes in chloroform at room temperature) and it is resistant to hydrogenation. Palladium or platinum catalysts in alcohol, ethyl acetate, or acetic acid with hydrogen at one atmosphere pressure have no effect at temperatures up to 80°. Hydrogenation of the molecular compound occurs with uptake of 2·7 mols. of hydrogen in 7 hours at 80° in the presence of platinum in acetic acid plus hydrochloric acid (cf. Windaus, Linsert, and Eckhardt, *Annalen*, 1938, **534**, 22), but the resulting mixture has not been separated. The very slight possibility that the double bond is in the recognised hindered positions, 7 : 8, 8 : 9, or 8 : 14, is ruled out by the observation that the acetates of (A) and (B) are unchanged by treatment with hydrogen chloride in chloroform, which causes migration of such bonds to the 14 : 15-position (Heilbron and Wilkinson, *J.*, 1932, 1708; Schenck, Buchholz, and Wiese, *Ber.*, 1936, **69**, 2696).

One hydroxyl group must be in the 3-position, since the reactant enol acetate (I) has an oxygen atom at that position. The molecular compound reacts extremely slowly with lead tetra-acetate in acetic acid ($k_{20°} \approx 0{\cdot}001$ l. mole^{-1} min.$^{-1}$). This is indication of a *trans*-α-glycol structure [cf. cholestane-3$\tilde{\beta}$: 5α : 6β-triol, $k \approx 0{\cdot}002$, and cholestane-3β : 5α : 6α-triol, $k = 72{\cdot}6$ (Criegee, *Ber.*, 1932, **65**, 1770)], and suggests a 2 : 3- or a 3 : 4-diol. The diols are unchanged by boiling alcoholic hydrochloric acid for several hours (see Rosenheim and Starling, *J.*, 1937, 377, and Barton and Rosenfelder, *J.*, 1951, 1048, on the relative ease of *cis*- and *trans*-elimination of water by ionic mechanisms), and neither diol will condense with acetone under the influence of hydrogen chloride. The absence of colour reactions which depend upon dehydration is also noteworthy (see Experimental). All these observations are in accord with a *trans*-α-glycol structure. The molecular compound yields no colour with tetranitromethane in chloroform, which is in keeping with the presence of an allylic alcohol grouping (cf. Ruzicka, Huyser, Pfeiffer, and Seidel, *Annalen*, 1929, **471**, 25; Mancera, Rosenkranz, and Djerassi, *J. Org. Chem.*, 1951, **16**, 192).

Though the evidence discussed above is insufficient for a final decision to be made, it is possible that the diols (A) and (B) are the unknown *trans*-cholest-5-ene-3 : 4-diols. However, it should be pointed out that since the diols (A) and (B) have not yet been identified, there is no guarantee that the cholestane skeleton of the original enol acetate is necessarily unchanged. The final determination of the structures of the diols, and the problem of the mechanism of their formation, await future work.

Experimental

The Molecular Compound.—A solution of cholestenone enol acetate (10·0 g.) in ether (100 ml.) was added during 10 minutes to a stirred solution prepared from lithium aluminium hydride (4·0 g.) in ether (150 ml.) and aluminium chloride (20 g.) in ether (50 ml.) (the precipitate of lithium chloride was previously removed by filtration). The solution refluxed perceptibly during the addition, after which external heat was applied for 2 hours. The mixture was cooled to 0° and decomposed by the gradual addition of acetone (30 ml.) and ether (200 ml.). The colourless ethereal solution was washed with sodium hydroxide solution and water. Removal of the ether yielded a colourless oil, which was dissolved in light petroleum (b. p. 40—60°; 100 ml.) and kept at 0° overnight. The white solid (4·5 g.) which separated was crystallised several times from methanol–ethanol (5 : 1), to yield the molecular *compound* as colourless irregular plates, m. p. 196—197°, $[\alpha]_D^{16}$ −47° (*c*, 0·5 in chloroform) (Found : C, 80·6, 80·1; H, 11·4, 11·4. $C_{27}H_{46}O_2$ requires C, 80·5; H, 11·5%. A weak bluish-purple colour is produced in the Liebermann–Burchard test, and no colour develops on treatment with trichloroacetic acid in chloroform (Rosenheim reaction). The compound does not yield an insoluble digitonide with digitonin in alcohol.

The light petroleum mother-liquor from the above compound was chromatographed through alumina. Evaporation of the light petroleum eluate yielded a colourless oil (1·4 g.) which crystallised. Recrystallisation from aqueous acetone yielded cholest-4-ene as colourless needles, m. p. 78—79° unchanged by admixture with an authentic specimen and $[\alpha]_D^{18}$ +69° (*c*, 0·7 in chloroform) (Found : C, 87·3; H, 12·2. Calc. for $C_{27}H_{46}$: C, 87·6; H, 12·4%). The dibromide separated from acetone as colourless plates, m. p. 116—117° (Mauthner, *Monatsh.*, 1907, **28**, 1113; Barton and Rosenfelder, *J.*, 1951, 1048; Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402). The alumina column contained an upper pale yellow band, which was eluted with benzene, to yield cholest-4-en-3-one, m. p. and mixed m. p. 77—78°.

Epoxide of the Molecular Compound.—After 9 hours at 0°, 0·347 g. of the molecular compound in chloroform reacted with 0·102 g. of perbenzoic acid, corresponding to 0·86 of a double bond; after 24 hours, 0·347 g. reacted with 0·116 g. of perbenzoic acid, corresponding to 0·98 of a double bond.

A mixture of the molecular compound (0·5 g.), perbenzoic acid (0·2 g.), and chloroform (20 ml.) was kept at 0° for 24 hours. The solution was washed with aqueous sodium carbonate and water, dried, and evaporated. Trituration of the oily residue with light petroleum yielded a white solid (0·4 g.). Recrystallisation from a small amount of methanol, and then from light petroleum (b. p. 80—100°), yielded the *epoxide* as needles, m. p. 166°, $[\alpha]_D^{17}$ −15° (*c*, 0·5 in chloroform) (Found : C, 77·0; H, 11·1. $C_{27}H_{46}O_3$ requires C, 77·5; H, 11·0%).

Acetylation of the Molecular Compound.—The molecular compound (1·5 g.) was refluxed with acetic anhydride (15 ml.) and benzene (15 ml.) for 7 hours, and then evaporated under reduced pressure. The remaining colourless viscous oil was dissolved in the minimum volume of hot acetone and kept at 0° overnight. The colourless prisms (0·6 g.) were separated, washed with acetone, and recrystallised from acetone. This *diacetate* had m. p. 157—158° and $[\alpha]_D^{17}$ −53° (*c*, 1·0 in chloroform) (Found : C, 76·7, 76·5; H, 10·6, 10·4. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·35%).

The acetone mother-liquor was evaporated and the solid residue crystallised several times from methanol–acetone (2 : 1), to yield a *diacetate* (0·4 g.) as colourless plates, m. p. 112—113°, $[\alpha]_D^{14}$ −31° (*c*, 0·4 in chloroform) (Found : C, 76·7 ; H, 10·3%).

Diol (A).—The diacetate, m. p. 157—158° (0·2 g.), was heated under reflux for 1 hour with a solution of sodium hydroxide in water (3 ml.) and alcohol (10 ml.). The solution was cooled, to yield a solid *diol (A)* (0·12 g.), which separated from methanol as colourless elongated plates, m. p. 177—178°, $[\alpha]_D^{14}$ −64° (*c*, 0·4 in chloroform) (Found : C, 80·1, 80·3; H, 11·7, 11·4; active H, 0·54. $C_{27}H_{46}O_2$ requires C, 80·5; H, 11·5; 2 active H, 0·50%). The diol reacts with bromine in chloroform, but the bromide readily decomposes with loss of hydrogen bromide. The *dibenzoate*, prepared by treating the diol with benzoyl chloride in pyridine, separated from ethanol as slender colourless needles, m. p. 166—167°, $[\alpha]_D^{19}$ −90° (*c*, 3·7 in chloroform) (Found : C, 81·0; H, 9·15. $C_{41}H_{54}O_4$ requires C, 80·7; H, 8·9%).

Diol (B).—Hydrolysis of the diacetate, m. p. 112—113° (0·08 g.), under the conditions used for the other, yielded a *diol (B)* (0·04 g.) which separated from methanol as flat colourless needles, m. p. 179—180°, $[\alpha]_D^{18}$ −34° (*c*, 0·6 in chloroform) (Found : C, 80·1; H, 11·4; active H, 0·48%). The *dibenzoate* separated from acetone as small needles, m. p. 164—165°, $[\alpha]_D^{19}$ +23° (*c*, 2·1 in chloroform) (Found : C, 80·5; H, 9·2%).

The mixed m. p. of the diols (A) and (B) was 170—193°.

Hydrolysis of Mixed Acetates.—An equimolecular mixture of the above acetates on hydrolysis yielded a compound which separated from alcohol as colourless irregular plates, m. p. 196—197°, unchanged by admixture with the molecular compound.

Synthesis of the Molecular Compound from the Diols (A) and (B).—Recrystallisation of an equimolecular mixture of the diols (A) and (B) from alcohol yielded colourless irregular plates, m. p. 196—197°, unchanged by admixture with the molecular compound.

Reaction with Lead Tetra-acetate.—The reaction was carried out in purified acetic acid at room temperature and the rate followed according to Criegee's method (*Ber.*, 1931, **64**, 260). The following results were obtained.

	Concn. (mole/l.)			
	$Pb(OAc)_4$	Mol. compd.	Time (hours)	k (l. mole^{-1} min.$^{-1}$)
Initial	0·0238	0·0110	—	—
Final	0·0210	0·00825	161	0·0013
Initial	0·0266	0·0142	—	—
Final	0·0207	0·0083	329	0·0012

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